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The effect of real-time electronic monitoring of patient-reported symptoms and clinical syndromes in outpatient workflow of medical oncologists: E-MOSAIC, a multicenter cluster-randomized phase III study (SAKK 95/06)

Strasser, F ; Blum, D ; von Moos, R ; Cathomas, R ; Ribi, K ; Aebi, S ; Betticher, D ; Hayoz, S ; Klingbiel, D ; Brauchli, P ; Haefner, M ; Mauri, S ; Kaasa, S ; Koeberle, D

Abstract: BACKGROUND: Patients with advanced, incurable cancer receiving anticancer treatment often experience multidimensional symptoms. We hypothesize that real-time monitoring of both symptoms and clinical syndromes will improve symptom management by oncologists and patient outcomes. PATIENTS AND METHODS: In this prospective multicenter cluster-randomized phase-III trial, patients with incurable, symptomatic, solid tumors, who received new outpatient chemotherapy with palliative intention, were eligible. Immediately before the weekly oncologists' visit, patients completed the palm-based E-MOSAIC assessment (Edmonton-Symptom-Assessment-Scale, 3 additional symptoms, estimated nutritional intake, body weight change, Karnofsky Performance Status, medications for pain, fatigue, nutrition). A cumulative, longitudinal monitoring sheet (LoMoS) was printed immediately. Eligible experienced oncologists were defined as one cluster each and randomized to receive the immediate print-out LoMoS (intervention) or not (control). Primary analysis limited to patients having uninterrupted (>4/6 visits with same oncologist) patient-oncologist sequences was a mixed model for the difference in patients global quality of life (G-QoL; items 29/30 of EORTC-QlQ-c30) between baseline (BL) and week 6. Intention-to-treat (ITT) analysis included all eligible patients. RESULTS: In 8 centers, 82 oncologists treated 264 patients (median 66 years; overall survival intervention 6.3, control 5.4 months) with various tumors. The between-arm difference in G-QoL of 102 uninterrupted patients (intervention: 55; control: 47) was 6.8 (P = 0.11) in favor of the intervention; in a sensitivity analysis (oncologists treating 2 patients; 50, 39), it was 9.0 (P = 0.07). ITT analysis revealed improvement in symptoms (difference last study visit-BL: intervention -5.4 versus control 2.1, P = 0.003) and favored the intervention for communication and coping. More patients with high symptom load received immediate symptom management (chart review, nurse-patient interview) by oncologists getting the LoMoS. CONCLUSION: Monitoring of patient symptoms, clinical syndromes and their management clearly reduced patients' symptoms, but not QoL. Our results encourage the implementation of real-time monitoring in the routine workflow of oncologist with a computer solution.

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The effect of real-time electronic monitoring of patient-reported symptoms and clinical syndromes in outpatient workflow of medical oncologists: E-MO*S*AIC, a multicenter cluster-randomized phase III study (SAKK 95/06)

F. Strasser[1,*], D. Blum[1,2,*], R. von Moos[3], R. Cathomas[3], K. Ribi[4], S. Aebi[5], D. Betticher[6], S. Hayoz[7], D. Klingbiel[7], P. Brauchli[7], M. Haefner[8], S. Mauri[9], S. Kaasa[2], D. Koeberle[10], on behalf of Swiss Group for Clinical Cancer Research (SAKK)

[1]Oncological Palliative Medicine, Clinic Oncology/Hematology, Dept. Internal Medicine and Palliative Center, Cantonal Hospital St. Gallen, St, Gallen, Switzerland

[2]European Palliative Research Centre, NTNU, and St Olavs University Hospital Trondheim, Trondheim, Norway

[3]Oncology, Cantonal Hospital Chur, Chur, Switzerland

[4]IBCSG, Bern, Switzerland

[5]Oncology, University Hospital Bern, Bern Switzerland

[6]Oncology, Cantonal Hospital Fribourg, Fribourg, Switzerland

[7]SAKK Coordinating Center, Bern, Switzerland

[8]Oncology, Bülach, Switzerland

[9]Oncology, Cantonal Hospital Lugano, Lugano, Switzerland

[10]Clinic Oncology/Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Corresponding Author: Dr. Florian Strasser, Clinic Oncology & Hematology, Dept. Internal Medicine and Palliative Center, Cantonal Hospital St. Gallen, Rorschacherstrasse 95, 9007 St.Gallen, Switzerland, Email: florian.strasser@kssg.ch, Telephone: +41 71 4941179

[*]both authors contributed equally to the paper.

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Key message:

Monitoring of symptoms of advanced cancer patients has little impact on patient outcomes. When symptoms are monitored with clinical syndromes in oncologist's routine workflow, facilitated by an electronic solution, symptom control improves. Improved symptom management suggests behavioral changes. Real time monitoring of a combination of patient reported outcomes and clinical data is promising.

Abstract

Background:
Patients with advanced, incurable cancer receiving anticancer treatment often experience multidimensional symptoms. We hypothesize that real-time monitoring of both symptoms and clinical syndromes will improve symptom management by oncologists and patient outcomes.

Patients and Methods:
In this prospective multicenter cluster-randomized phase-III trial patients with incurable, symptomatic, solid tumors, who received new outpatient chemotherapy with palliative intention, were eligible. Immediately before the weekly oncologists' visit patients completed the palm-based E-MO*S*AIC assessment (Edmonton-Symptom-Assessment-Scale, ≤3 additional symptoms, estimated nutritional intake, body weight change, Karnofsky Performance Status, medications for pain, fatigue, nutrition). A cumulative, longitudinal monitoring sheet (LoMoS) was printed immediately. Eligible experienced oncologists were defined as one cluster each and randomized to receive the immediate print-out LoMoS (intervention) or not (control). Primary analysis limited to patients having uninterrupted (>4/6 visits with same oncologist) patient-oncologist sequences was a mixed model for the difference in patients global quality of life (G-QoL; items 29/30 of EORTC-QlQ-c30) between baseline (BL) and week 6. Intention-to-treat analysis included all eligible patients.

Results
In 8 centers, 82 oncologists treated 264 patients (median 66y; overall survival intervention 6.3, control 5.4 mts) with various tumors. The between-arm difference in G-QoL of 102 uninterrupted patients (intervention: 55; control: 47) was 6.8 (p=0.11) in favour of the intervention, in a sensitivity analysis (oncologists treating ≥2 patients; 50, 39) it was 9.0 (p=0.07). Intention-to-treat analysis revealed improvement in symptoms (difference last study visit - BL: intervention -5.4 versus control 2.1, p= 0.003) and favoured the intervention for

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communication and coping. More patients with high symptom load received immediate symptom management (chart review, nurse-patient interview) by oncologists getting the LoMoS.

Conclusion

Monitoring of patient symptoms, clinical syndromes and their management clearly reduced patients' symptoms, but not QoL. Our results encourage the implementation of real-time monitoring in the routine workflow of oncologist with a computer solution.

Key words:

Symptom monitoring, clinical benefit, electronic assessment, decision making, integration oncology & palliative care, chemotherapy palliative intention

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Introduction

Patients with advanced, incurable cancer experience multiple, fluctuating, and multidimensional symptoms, many of which are under-recognized and undertreated. Oncologists are often the central care providers, but in different health care systems their professional roles may differ substantially, influenced also by availability of nurses and other staff.[1] Anticancer treatments for patients with advanced incurable cancer are often intended to stabilize or improve quality of life and alleviate symptoms Symptom control is one key component of palliative care.[2, 3]

In prior studies, monitoring of symptoms (patient-reported outcomes (PROs) by use of computerized systems enhanced the likelihood of symptoms assessment [4] and communication,[5] but did not improve outcomes.[6, 7] Isolated symptom information is therefore not consistently used by oncologists.[8] When symptom monitoring is amended by nurse-delivered patient education and coaching or self-management support, distress as an outcome parameter could be improved.[9, 10] We added clinical data and pharmacological management to patient reported symptoms in order to mirror oncologists' routine practice.

E-MOSAIC (*e*lectronic *mo*nitoring of *s*ymptoms and *s*yndromes *a*ssociated w*i*th *c*ancer) assessment was developed on a PALM device. Feasibility and reliability was reported previously.[11]

The E-MOSAIC assessment was done by all patients immediately before weekly oncology outpatient visits using a handheld computer. A printed colored comprehensive *lo*ngitudinal *mo*nitoring *s*heet (LoMoS) was immediately given to the oncologists in the intervention group.

In this cluster-randomized controlled multicenter trial we tested the effects of the E-MOSAIC intervention in patients with incurable cancer getting a new line of chemotherapy with a palliative intention.

Methods

This multicenter trial (NCT00477919) was conducted in accordance with the Declaration of Helsinki and the Guidelines of Good Clinical Practice issued by ICH. It was approved by

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the local ethics committees of all centers. Patients and physicians gave written informed consent.

Study population

Eligible patients received anticancer treatment with palliative intent and an expected tumor response rate ≤ 20%, on a weekly, biweekly, or continuous schedule in the outpatient setting. Patients had to be clinically not cognitively impaired; symptomatic defined as at least one Edmonton symptom assessment score (ESAS) symptom score ≥3/10. Patients were characterized for age, gender, tumor type, Education (basic primary/secondary vs higher), Comorbidities (severe symptomatic requiring actual treatment).

Oncologists and needed to have training in internal medicine and ≥1 year experience in medical oncology which includes typically basic symptom management and were required to independently perform medical interventions and to have completed a communication skills course.

Trial design

A cluster-randomized design with the individual oncologists constituting clusters was applied to test the 6-weeks E-MO*S*AIC intervention. This design was chosen to avoid the potential bias of learning effects and under the assumption that physicians treat all patients the same.

At enrolment each participating physician was randomly allocated to one of the 2 arms at 1:1 ratio stratified according to institution using the block randomization method. Randomization of physicians and registration of patients was performed via fax at the SAKK coordinating center.

Intervention

The intervention was previously described in detail.[12] All patients were seen first by nurses who possibly assisted with the E-MO*S*AIC assessment. The LoMoS contains weekly cumulative quantitative information on patients' symptoms, clinical data and medications

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(ESAS, ≤3 additional symptoms, estimated nutritional intake, body weight change, Karnofsky performance status, medications for pain [daily dose of analgesics converted to oral morphine equivalent dose; co-analgesics], fatigue [methylphenidate, erythropoietin], and nutrition [oral nutritional supplements]). It was printed out immediately and delivered to the oncologists in the intervention arm. No specific education and no treatment guidelines were provided. The LoMoS was removed from the charts in order to maintain blinding. The staff assessing the patients was blinded to the randomization.

Primary endpoint

The primary endpoint was change in Global Quality of Life (G-QoL), measured as the difference in G-QoL between baseline and after last study visit (6 weeks). The change in QoL was assessed using the composite score of questions 29 and 30 of the EORTC-QLQ-C30.

Secondary Endpoints

The secondary endpoints: symptoms, symptom complexity, KPS, nutrition and oncologists' symptom management performance were measured at baseline and then weekly. Communication and patient coping and treatment burden were assessed at baseline and at weeks 3 and 6.

Symptoms: Symptom distress score: The sum of the nine ESAS items as used in the original publication.[13] *Symptom complexity* was defined as ≥3 symptoms with ≥6/10, with the exception of fatigue and anorexia (threshold ≥9/10). *Function* was assessed by KPS and physical and emotional function scores from EORTC-QLQ-C30, *Nutrition* by the symptom appetite, patient-perceived nutritional intake and weight loss.

To measure *oncologists' symptom management performance,* all diagnostic, therapeutic or coordinative interventions performed by the oncologist to alleviate multidimensional suffering of patients and family members were collected from routine medical charts (Structured Chart Review, SyMPeC) [14] and by nurses asking patients about last weeks' oncologists interventions (visit form). The number of visits with a symptom load above the

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mentioned threshold without immediate oncologists' intervention was assessed. Immediate intervention was defined as either ticking "yes" on the visit form or as derived by SyMPeC.

Patients' estimation of the *patient-physician communication* were assessed by a previously published but not specifically validated scale (80-100)[15]. The indicators for patients' subjective *coping effort* and *burden of treatment* have been validated.[16, 17].

Data analysis and statistical considerations

Half a standard deviation was chosen as a clinically meaningful difference in G-QoL between the study arms [18]. Assuming an overall variance of 400 an intra-cluster correlation coefficient (ICC) 0.05 and cluster size 12 evaluable patients per physician, 240 evaluable patients were needed to show the clinically relevant difference with power 0.8 and significance level 0.05 using a mixed model. In the interim analysis it was seen that the cluster sizes were smaller, thus the sample size was re-estimated with four patients per cluster to a total of 168 evaluable patients. To compensate for attrition it was increased to 264 patients.

The primary endpoint included all patients having uninterrupted visits by the same oncologist, defined by strict, predefined criteria such as a screening threshold of cognitive impairment (see ***Figure 1***).[19] A supportive analysis was performed based on the intention-to-treat (ITT) population, in which all eligible patients were included if the QoL data at baseline and at 6 months as well as the predefined covariates were available. A sensitivity analysis with oncologist treating more than one patient was done.

For the primary endpoint a priori defined covariates (education, tumor type, predominant symptom, anxiety, complexity, hospitalizations) and the baseline G-QoL value were included in the analysis model. Due to clustering structure, comparisons of different outcomes between treatment arms were analyzed by mixed models. All secondary endpoints were analyzed based on the ITT population using all available assessments for the respective endpoint. No imputation for missing data was performed. For endpoints with continuous

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values, linear mixed models were applied, for endpoints with categorical or binary values, nonlinear mixed models or generalized estimating equations. The oncologist was included as random effect. All statistical tests were done two-sided at a significance level of 0.05. As no adjustment for multiple testing was applied for analyses other than the primary endpoint analysis, they were exploratory. All analyses were performed using SAS 9.2 (SAS Institute) and R 2.15.2 (http://www.r-project.org).

Results

Eight centers in Switzerland participated. 82 oncologists were randomized. Between July 2007 and January 2012 264 patients were included, median age was 66 years. In ***Table 1*** the patients and oncologists are characterized with respect to socio-demographic variables and patients' disease and treatment-related variables. The most frequent applied chemotherapies were platinum compounds and taxanes, followed by pyrimidines (gemcitabine, 5-FU). Most often double-combination chemotherapies were used, targeted therapies only in few cases often in combination (Cetuximab, Bevacizumab).

The patient flow is summarized in ***Figure 1***. The median overall survival was 5.78 months (control: 5.39 months, intervention 6.28 months; log-rank p-value=0.9). The median follow up time was 3.39 months (95% confidence interval 3.22 to 3.48).

Global Quality of Life

For the primary analysis 102 (39%) patients were included. Main reasons for non-inclusion were attrition (missing QoL measurement at week 6, 78 patients), less than 4 physician visits (44 patients) and insufficient cognitive function (58 patients) (***Figure 1***).

The standard deviation of difference in G-QoL between baseline and week 6 over all patients was 21.92, thus a difference between the two study arms of 10.96 was considered clinically meaningful.

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The between-arm difference was 6.84 [-1.65, 15.33] (p=0.1) in favor of the intervention arm. The mixed model for the primary endpoint with the solution for fixed effects is displayed in ***Table 2.*** Of the preselected covariates only baseline G-QoL and hospitalization (p=0.09) had a significant effect on G-QoL (p=0.0008). The ICC could not be calculated for this model because of numerical problems due to the high number of physicians with only one patient.

For the ITT analysis of 177 patients included the ICC was 0.04 and the between-arm difference was 5.95 [-0.20, 12.09] (p=0.06) in favor of the intervention arm.

The sensitivity analysis with 41 oncologists (39 patients; control, 50 intervention) provided similar results as the original model: The between-arm difference was 8.96 [-0.88, 18.81] (p=0.07) in favor of the intervention arm. The ICC was 0.03.

Symptoms

The differences of symptoms and the syndromes fatigue and nutrition between baseline and after last study visit are listed in ***Table 3.***

The change in symptom distress score between first and last visit was compared between the two treatment arms using a linear mixed model including baseline symptom distress score as covariate and oncologist as random effect. There was a significant (p=0.003) difference of 5.70 [95% CI 1.96, 9.43] in favor of the intervention arm.

Symptom Management Performance

The difference between the arms showed a trend favoring the intervention arm (p=0.06). There were 71 (52%) patients in the intervention arm and 40 (38%) patients in the control arm, who had symptom management intervention in visits with a symptom load above a defined threshold.

Communication, coping and treatment burden

The differences between arms at baseline and at last study visit are displayed in ***Table 4*** **in the supplementary material.**

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Discussion

The E-MOSAIC intervention incorporates clinical and management data in addition to patient-reported symptom information into the oncologist routine workflow. The significant improvement in symptom distress of the overall intervention and the observed trends of improved symptom management, communication, and coping is promising. However, the hypothesized effect on global QoL was not reached. However, the hypothesized effect on global QoL for the strictly defined per protocol population of uninterrupted single oncologist-patient visits was not reached. This analysis was underpowered and too ambitious. Therefore, the intervention may be interpreted as an intervention applicable for mid-size cancer centers and may limit generalizability to single oncologist practices.

Our intervention showed positive effects on the specifics of the intervention (symptoms and symptom management). This is in line with other trials, where interventions such as end-of-life preparation did not improve depression, but improved communication at end-of-life.[20] This finding reflects the concept of mechanism based interventions, rather than a complex intervention.

Even though there was a clear improvement of overall symptoms, we could not identify specific symptoms, which were more responsive to the intervention than others, which is consistent with published trials. [9, 10] According to our definition, patients with more symptoms and higher symptom scores had higher symptom complexity. Previous randomized controlled trials on specialist palliative care seem also to be most effective in complex situations.[2, 21]. In general the symptom burden of our population is comparable with other symptom epidemiological data.[22]

In daily practice it is challenging for oncologists to differentiate cancer related symptoms and therapy associated toxicity. Data from anticancer clinical trials usually mix toxicity and quality-of-life.[23] Therefore we cannot assume that E-MO*S*AIC improved symptoms due to reduction of toxicity. The types of chemotherapy and the response rates were similar in both arms.

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Limitations:

Our results might be limited to the specific setting with weekly visits, oncologists' education including palliative care and communication competences, the selected group of patients living half a year and flexibility of operational and financial circumstances. The study did not have any focused or structured patient education nor provide nurse-led symptom counselling or patient empowerment, and our care settings did not include routine joint nurse-physician visits.

A learning effect is possible by the teams with increasing use of the E-MO*S*AIC and LoMoS data. In an attempt to prevent this, LoMoS sheets were removed from the charts.

The lack of full blinding may limit the results. Standard care without E-MO*S*AIC assessment was not compared to the two arms.

The number of patients in the primary analysis requiring uninterrupted sequences and intact cognitive function at every visit was lower than anticipated, which resulted in a loss of statistical power. Several physicians included only one patient. The reality of oncology clinics with physicians working in rotations, part-time and being on leave hindered the continuous care over a longer time period. However, the sensitivity analysis excluding those clusters of only one patient per physician confirmed the results of the primary analysis. The observed attrition rate of 32% in the intervention and 27% in the control arm occurs commonly in trials of advanced cancer patients. [24]

Future research should focus on the questions whether provision of clinical practice recommendations by education, decision aids, or computer based decision support systems would further enhance patient care.[25] Our data may encourage a more patient-centred research culture.

Our results encourage the implementation of combined monitoring of symptoms and related clinical parameter and medications in the routine workflows of oncologist in an integrated and computer interface solution (e.g. web-based, e-health record), which suggest also available professional or proxies patient support.[5]

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Conclusion

The provision of real-time combined information of advanced cancer patients' symptoms, related clinical syndromes and their medication in the routine work flow of oncologists resulted in promising effects concerning symptoms and symptom management.

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David Blum and Florian Strasser had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosure:

The authors have declared no conflicts of interest.

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Legends

Figure 1: CONSORT Diagram for cluster randomized trials

Table 1: Patients and oncologists characterization with respect to sociodemographic variables and patients' disease and treatment-related variables for each arm

Table 2: Mixed model for the primary endpoint with the solution for fixed effects

Table 3: ESAS, symptom, function, nutrition, complexity and symptom management performance

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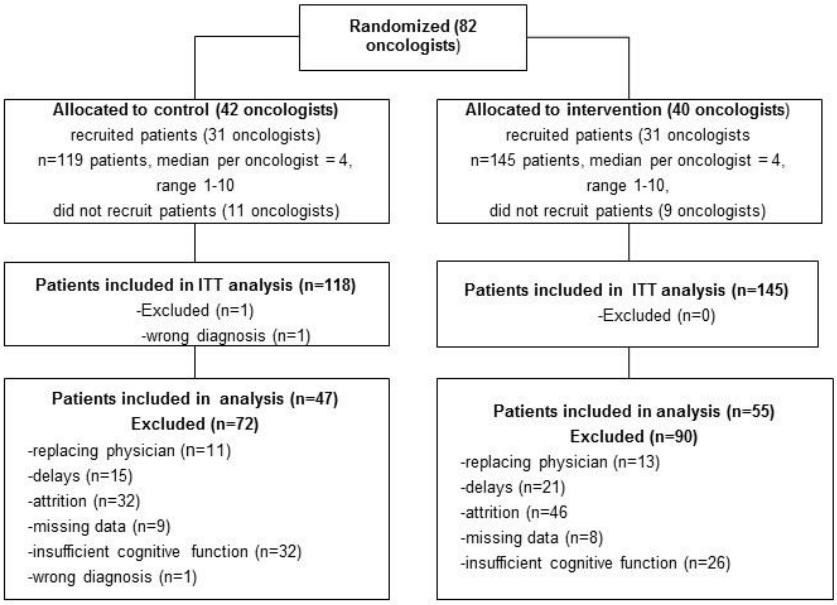
Figure 1: CONSORT diagram



Patients were excluded from the PP analysis if they violated one of the inclusion criteria for primary analysis:

- having less than 4 physicians' visits within the 6 weeks period, having more than 1 visit with a replacing physician
- having insufficient cognitive function, having missing QoL at baseline or at week 6
- having more than 14 days from registration to baseline examination and being longer eligible
- having the last study visit more than 14 days delayed
- having the last visit less than 14 days delayed but less than 2 visits or contact to replacing physician in between

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Table 1 Demographics of patients and oncologists

PATIENTS				
Variable	**Control** ***(N=119)***		**Intervention** ***(N=145)***	
Gender				
. Female	47	(39%)	51	(35%)
. Male	72	(61%)	94	(65%)
Age (in years) (median, min, max)	67.3	(35.3, 84.3)	65.1	(39.9, 84.3)
Education				
. Basic education	94	(79%)	104	(72%)
. Additional education	24	(20%)	40	(28%)
. Missing	1	(1%)	1	(1%)
Tumor type				
NSCLC	25	21%	25	17%
Colorectal cancer	18	5%	20	14%
Prostate carcinoma	13	11%	10	7%
Breast cancer	12	10%	15	10%
Pancreatic carcinoma	10	8%	20	14%
Bladder cancer	6	5%	3	2%
Ovarian cancer	6	5%	4	3%
Unknown primary cancer	4	3%	9	6%
Gastric cancer	4	3%	4	3%
SCLC extensive disease	3	3%	1	1%
Upper GI cancer	3	3%	4	3%
Oesophageal cancer	3	3%	2	1%
Metastatic melanoma	2	2%	2	1%
Renal cell carcinoma	2	2%	2	1%
Mesothelioma	2	2%	3	%
Sarcoma	2	2%	2	1%
Biliary tract carcinoma	1	1%	1	1%
Glioblastoma	0	0%	2	1%
H&N cancer	0	0%	7	5%
Other	0	0%	4	3%
Comorbidity[1]				
. No	101	(85%)	107	(74%)
. Yes	16	(13%)	34	(23%)
Oncologist				
Variables	A *(N=42)*		B *(N=40)*	
	n	**(%)**	***n***	**(%)**
Gender				
. Female	13	(31%)	20	(50%)
. Male	29	(69%)	20	(50%)

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Table 1 Demographics of patients and oncologists (Continued)

Variable	**Control *(N=119)***		**Intervention *(N=145)***	
Age (in years) (median, min, max)	37.0	(30, 56)	37.0	(31, 58)
Mother tongue				
. French	1	(2%)	1	(3%)
. French and German	2	(5%)	0	(0%)
. German	35	(83%)	35	(88%)
. Italian	3	(7%)	3	(8%)
. Romanian (Arm A)/English (Arm B)	1	(2%)	1	(3%)

1. Defined as presence of severe symptomatic comorbidity requiring actual treatment.

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Table 2: Mixed model for the primary endpoint including patients having uninterrupted visits with the same oncologist (n=102): Solution for fixed effects

Effect	Categories	Estimate	Standard Error	Confidence Interval	*p-value*
Randomization Arm		-6.9	4.2	[-15.3, 1.7]	*0.1*
Baseline G-QoL		-0.6	0.1	[-0.8, -0.2]	*0.001*
Predominant Symptom	Anxiety	1.6	24.2	[-47.7, 51.0]	*0.9*
	Appetite	7.9	13.0	[-18.6, 34.5]	*0.5*
	Shortness of breath	-15.5	13.7	[-43.4, 12.4]	*0.3*
	Tiredness	-9.0	11.4	[-32.4, 14.3]	*0.4*
	Pain	-3.8	13.3	[-31.0, 23.3]	*0.8*
	Drowsiness	7.4	21.8	[-37.0, 51.7]	*0.7*
	Wellbeing	1.4	14.2	[-27.6, 30.3]	*0.9*
	Nausea	0	.	.	.
	Other	-9.7	10.1	[-30.2, 10.9]	*0.3*
Complexity	0	7.74	5.7	[-3.9, 19.4]	*0.2*
	1 *	0	.	.	.
Anxiety	0	13.4	20.3	[-28.1, 54.9]	*0.5*
	1 **	0	.	.	.
Hospitalization	No	11.3	6.4	[-1.7, 24.4]	*0.09*
	Yes	0	.	.	.
Education	Baseline education	2.7	5.1	[-7.7, 13.1]	*0.6*
	Additional education	0	.	.	.
Tumor Type	Renal cell carcinoma	46.6	18.7	[8.6, 84.6]	*0.02*
	Pancreatic carcinoma	14.4	14.3	[-14.7, 43.4]	*0.3*
	Mesothelioma	7.3	19.8	[-33.2, 47.7]	*0.7*
	Prostate carcinoma	17.7	13.8	[-10.4, 45.8]	*0.2*
	NSCLC	3.1	13.2	[-23.8, 30.1]	*0.8*
	Colorectal cancer	18.3	13.5	[-9.1, 45.8]	*0.2*

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Table 2: Mixed model for the primary endpoint including patients having uninterrupted visits with the same oncologist (n=102): Solution for fixed effects (Continued)

Effect	Categories	Estimate	Standard Error	Confidence Interval	*p-value*
Tumor Type (Continued)	Upper GI cancer	26.8	16.1	[-6.0, 59.7]	*0.1*
	Bladder cancer	37.7	16.9	[3.2, 72.2]	*0.03*
	Sarcoma	-2.4	19.3	[-41.8, 37.0]	*0.9*
	Unknown primary cancer	18.2	14.9	[-12.3, 48.6]	*0.2*
	Breast cancer	10.0	14.3	[-19.2, 39.3]	*0.5*
	Ovarian cancer	8.6	15.7	[-23.5, 40.8]	*0.6*
	H&N cancer	2.5	16.0	[-30.1, 35.0]	*0.9*
	Biliary tract carcinoma	30.6	23.1	[-16.6, 77.8]	*0.2*
	Gastric cancer	18.0	16.7	[-16.1, 52.1]	*0.3*
	Esophageal cancer	4.2	18.0	[-32.5, 40.9]	*0.8*
	Other situation	0	.	.	.
Intercept		-8.6	26.1	[-61.4, 44.2]	*0.7*

* 1 defined: >=3 symptoms (of the 9 ESAS Symptoms and 1 free choice) above threshold (fatigue and anorexia >=9/10, other symptoms >=6/10) in baseline visit
** 1 defined: >=6/10 in baseline visit

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Table 3: Symptoms, Function, Nutrition, Complexity, Symptom Management Performance

Variable	Control (N=118)			Intervention (N=145)		
	n	**median**	**(Q1, Q3)**	***n***	**median**	**(Q1, Q3)**
Symptom distress score[1]						
. first visit	*96*	25.9	(16.9, 36.1)	*112*	29.0	(20.3, 39.0)
. last visit	*96*	28.7	(16.0, 41.9)	*112*	24.0	(12.0, 35.9)
. change first to last visit	*96*	2.1	(-7.0, 10.4)	*112*	-5.4	(-13.6, 3.9)
	Difference between treatment arms[2]*: 5.70 [95% CI 1.96, 9.43]*					
Pain[3]						
. first visit	*96*	12.8	(3.7, 31.2)	*112*	16.2	(5.0, 32.0)
. last visit	*96*	21.4	(5.5, 41.9)	*112*	11.7	(3.8, 34.2)
. change first to last visit	*96*	0.8	(-5.8, 15.9)	*112*	-0.5	(-8.3, 4.2)
Fatigue[3]						
. first visit	*96*	45.8	(22.6, 72.4)	*112*	38.3	(17.6, 62.2)
. last visit	*96*	39.7	(23.7, 69.3)	*112*	39.2	(14.4, 57.2)
. change first to last visit	*96*	0.0	(-7.4, 9.4)	*112*	-1.0	(-11.7, 9.6)
Drowsiness[3]						
. first visit	*96*	28.7	(11.9, 61.9)	*112*	27.3	(14.2, 49.8)
. last visit	*96*	29.3	(12.5, 57.4)	*112*	25.8	(8.9, 49.8)
. change first to last visit	*96*	-1.3	(-10.5, 4.9)	*112*	-1.0	(-12.4, 3.3)
Nausea[3]						
. first visit	*96*	7.1	(2.2, 16.6)	*112*	6.7	(1.9, 21.8)
. last visit	*96*	7.0	(2.8, 17.0)	*112*	6.1	(2.2, 18.3)
. change first to last visit	*96*	0.3	(-3.9, 3.1)	*112*	0.0	(-2.9, 2.8)
Appetite[3]						
. first visit	*95*	38.3	(13.9, 57.5)	*112*	26.9	(8.3, 51.7)
. last visit	*96*	29.7	(10.7, 59.9)	*112*	22.2	(4.4, 49.3)
. change first to last visit	*95*	0.0	(-12.7, 7.8)	*112*	-0.4	(-11.1, 4.4)
Shortness of breath[3]						
. first visit	*94*	12.7	(4.4, 41.1)	*112*	8.6	(3.2, 28.6)
. last visit	*96*	13.7	(4.9, 46.1)	*111*	10.6	(4.0, 28.8)
. change first to last visit	*94*	0.0	(-2.7, 7.2)	*111*	0.0	(-5.4, 4.4)
Depression[3]						
. first visit	*96*	7.8	(2.6, 16.9)	*112*	6.5	(2.2, 15.7)
. last visit	*96*	9.3	(3.3, 23.1)	*112*	5.6	(2.5, 17.2)
. change first to last visit	*96*	0.4	(-2.8, 7.9)	*112*	0.0	(-3.2, 2.3)
Anxiety[3]						
. first visit	*96*	7.3	(3.1, 17.8)	*112*	7.6	(2.7, 16.2)
. last visit	*96*	8.3	(3.3, 24.3)	*112*	6.6	(2.8, 18.3)
. change first to last visit	*96*	0.3	(-2.2, 3.9)	*112*	0.0	(-2.9, 2.8)
Wellbeing[3]						
. first visit	*94*	42.5	(22.8, 52.0)	*112*	30.3	(15.1, 51.8)
. last visit	*96*	35.2	(18.1, 54.5)	*112*	34.1	(14.2, 51.6)
. change first to last visit	*94*	0.0	(-14.3, 6.2)	*112*	-0.6	(-10.8, 11.8)
Function						
KPS[4]						
. first visit	*96*	75.0	(65.0, 90.0)	*112*	80.0	(70.0, 90.0)
. last visit	*96*	70.0	(60.0, 90.0)	*112*	70.0	(60.0, 90.0)
. change first to last visit	*96*	0.0	(-10.0, 5.0)	*112*	0.0	(-10.0, 10.0)
	Difference between treatment arms[2]*: 1.97 [95% CI -3.70, 7.64]*					

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Table 3: Symptoms, Function, Nutrition, Complexity, Symptom Management Performance (Continued)

Variable		Control (N=118)			Intervention (N=145)	
Function (continued)						
Physical Function[5]						
. first visit	*98*	33.3	(20.0, 46.7)	*109*	33.3	(20.0, 53.3)
. last visit	*67*	33.3	(20.0, 46.7)	*75*	26.7	(13.3, 46.7)
. change first to last visit	*67*	0.0	(-6.7, 13.3)	*75*	0.0	(-13.3, 6.7)
	Difference between treatment arms[2]: 5.16 [95% CI -1.46, 11.79]					
Emotional Function[5]						
. first visit	*99*	25.0	(16.7, 50.0)	*108*	33.3	(16.7, 50.0)
. last visit	*72*	25.0	(8.3, 41.7)	*76*	25.0	(8.3, 41.7)
. change first to last visit	*72*	0.0	(-16.7, 8.3)	*76*	-8.3	(-16.7, 8.3)
	Difference between treatment arms[2]: 4.76 [95% CI -1.09, 10.61]					
Nutrition	***n***	**median**	**(min, max)**	***n***	**median**	**(min, max)**
Weight (kg)						
. first visit	*75*	68.0	(57.6, 80.0)	*98*	68.5	(58.0, 79.0)
. last visit	*49*	70.0	(62.0, 79.0)	*55*	67.0	(58.0, 78.0)
. change first to last visit	*49*	0.1	(-1.0, 1.4)	*55*	0.3	(-1.0, 2.0)
	Difference between treatment arms[2]: 0.15 [95% CI -1.12, 1.41]					
Nutritional intake[6]						
. first visit	*96*	3.1	(1.1, 5.2)	*112*	3.7	(1.3, 5.8)
. last visit	*96*	3.2	(1.2, 5.5)	*111*	2.3	(0.5, 4.9)
. change first to last visit	*96*	0.0	(-1.4, 1.6)	*111*	-0.4	(-2.5, 0.9)
	Difference between treatment arms[2]: 0.68 [95% CI -0.01, 1.36]					
		n	**(%)**		***n***	**(%)**
Symptom Complexity[7]						
Complexity at baseline						
. non-complex case		*80*	(68%)		*103*	(71%)
. complex case		*33*	(28%)		*40*	(28%)
. Missing		*5*	(4%)		*2*	(1%)
Complexity at visit 6						
. non-complex case		*65*	(55%)		*87*	(60%)
. complex case		*24*	(20%)		*17*	(12%
. Missing		*29*	(25%)		*41*	(28%)
		n	**(%)**		***n***	**(%)**
Oncologist Symptom Management						
. No visit with a symptom load above a defined threshold[8] without immediate intervention		*40*	(34%)		*71*	(49%)
. At least 1 visit with a symptom load above a defined threshold without immediate intervention		*66*	(56%)		*66*	(46%)

1) Sum ESAS

2) Difference between treatment arms calculated using a linear mixed model including baseline as covariate and oncologist as random effect

3) ESAS 0 min (no problem)-100 max (max problem)

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4) Karnofsky Performance Scale
5) EORTC QLQ C30
6) Nutritional intake 0 as before disease, 10 nothing
7) Complexity defined as ≥3 symptoms with ≥6/10, with the exception of fatigue and anorexia (threshold ≥9/10)
8) Threshold defined as pain, depression, shortness of breath (≥6/10) and fatigue anorexia (≥9/10)
Note: For theses analyses only patients with at least 4 visits were included.

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Table 4: Communication, Decision making preference, Coping and Burden

Variable	Control (N=118)			Intervention (N=145)		
	n	median	(Q1, Q3)	n	median	(Q1, Q3)
Physician compassion[1]						
. baseline	96	33.5	(12.0, 69.5)	129	45.0	(18.0, 91.0)
. week 6	77	23.0	(10.0, 61.0)	93	20.0	(10.0, 58.0)
. change baseline to week 6	69	-4.0	(-22.0, 10.0)	85	-14.0	(-36.0, 8.0)
	Difference between treatment arms[2]: 0.80 [95% CI -16.49, 18.09]					
Physician attributes[2]						
Physician selfishness						
. baseline	108	4.0	(1.0, 9.0)	138	6.0	(2.0, 11.0)
. week 6	84	4.0	(2.0, 9.0)	98	4.0	(2.0, 9.5)
. change baseline to week 6	83	0.0	(-3.0, 3.0)	95	-1.0	(-6.0, 2.0)
Physician participation						
. baseline	108	5.0	(2.0, 10.5)	136	7.0	(3.0, 13.0)
. week 6	85	4.0	(2.0, 10.0)	97	4.0	(2.0, 11.0)
. change baseline to week 6	84	0.0	(-3.0, 2.0)	93	-1.0	(-6.0, 2.0)
Physician questions						
. baseline	109	5.0	(2.0, 10.0)	136	6.0	(3.0, 11.5)
. week 6	85	5.0	(1.0, 9.0)	99	4.0	(2.0, 8.0)
. change baseline to week 6	84	0.0	(-3.0, 3.0)	94	-1.0	(-7.0, 1.0)
Physician feelings						
. baseline	107	5.0	(2.0, 9.0)	136	6.0	(2.5, 12.0)
. week 6	82	4.0	(2.0, 9.0)	98	4.0	(2.0, 9.0)
. change baseline to week 6	81	0.0	(-3.0, 2.0)	94	-1.0	(-7.0, 3.0)
Physician interest						
. baseline	108	4.0	(2.0, 8.0)	137	6.0	(2.0, 10.0)
. week 6	84	4.0	(2.0, 8.0)	99	4.0	(2.0, 9.0)
. change baseline to week 6	83	0.0	(-3.0, 3.0)	97	-1.0	(-5.0, 2.0)
Physician relation						
. baseline	106	4.5	(2.0, 9.0)	135	7.0	(3.0, 14.0)
. week 6	83	4.0	(2.0, 9.0)	98	4.0	(1.5, 11.0)
. change baseline to week 6	81	0.0	(-3.0, 2.0)	94	-1.0	(-7.0, 1.0)
Physician satisfaction[4]						
. baseline	88	28.0	(27.0, 32.0)	122	28.0	(27.0, 31.0)
. week 6	61	28.0	(27.0, 30.0)	77	28.0	(27.0, 31.0)
. change baseline to week 6	52	0.0	(-2.0, 2.0)	68	0.0	(-1.0, 1.5)
	Difference between treatment arms[2]: -0.51 [95% CI -1.82, 0.79]					

Decision making preference[5]	n	%	n	%
Mismatch at baseline				
. missing	36	(31%)	31	(21%)
. no	38	(32%)	46	(32%)
. yes	44	(37%)	68	(47%)
Mismatch at week 3				
. missing	44	(37%)	49	(34%)
. no	32	(27%)	41	(28%)
. yes	42	(36%)	55	(38%)
Mismatch at week 6				
. missing	52	(44%)	66	(46%)
. no	32	(27%)	38	(26%)
. yes	34	(29%)	41	(28%)

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Coping and Burden	n	median	(Q1, Q3)	n	median	(Q1, Q3)
Coping with illness[6]						
. baseline	78	33.5	(19.0, 53.0)	95	42.0	(22.0, 61.0)
. week 6	84	36.5	(18.0, 58.0)	95	27.0	(13.0, 47.0)
. change baseline- week 6	77	1.0	(-7.0, 12.0)	92	8.0	(-2.5, 21.5)
	Difference between treatment arms[2]: 0.54 [95% CI 0.41, 0.67]					
Burden of treatment[7]						
. baseline	78	33.5	(15.0, 55.0)	91	33.0	(14.0, 53.0)
. week 6	85	36.0	(21.0, 58.0)	94	29.5	(11.0, 48.0)
. change baseline - week 6	78	-3.0	(-15.0, 8.0)	87	1.0	(-13.0, 18.0)
	Difference between treatment arms[2]: 0.52 [95% CI 0.39, 0.66]					

1) Patients' estimation of physicians' compassion (VAS, sum of 5 items, range 0-500, the lower the value, the better)
2) Difference between treatment arms calculated using a linear mixed model including baseline as covariate and oncologist as random effect
3) Patients' estimation of physicians' attributes (VAS, range 0-100, the lower the value, the better);
4) Sum of 7 items range 1-5, total range 7-35, the higher the value, the better;
5) Patients and physicians were assessed: 3 Categories were possible: 1)physician directed decision preference 2)patient-directed decision preference 3) shared decision making preference. If the patient's impression and the doctor's impression of the decision-making preferences fell into the same of these 3 categories, it was considered a match.
6) Linear analogue self-assessment (LASA)) ('no effort at all' – 'a great deal of effort)
7) Overall treatment burden ('not at all' – 'severely')

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